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ASSESSMENT OF RIGHT VENTRICULAR FUNCTION BY ECHOCARDIOGRAPHY IN PULMONARY HYPERTENSION

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CERTIFICATE

This is to certify that this dissertation entitled Assessment Of Right Ventricular Function By Echocardiography In Pulmonary Hypertension submitted by **Dr. V.Ravi** to The Tamil Nadu Dr. M. G. R. Medical University, Chennai is in partial fulfilment of the requirement for the award of DM Cardiology and is a bonafide research work carried out by him under direct supervision and guidance.

DEAN

Government Rajaji Hospital, and
Madurai Medical College Madurai

Prof .Dr .S.Palanichamy, M.D., D.M. M.D,D.M,

Professor and H.O.D
Department of Cardiology
Government Rajaji Hospital,
and Madurai Medical College
Madurai

DECLARATION

I, **Dr.V.Ravi** solemnly declare that I carried out this work on Assessment of Right Ventricular Function by Echocardiography in Pulmonary Hypertension at Department of Cardiology, Government Rajaji Hospital during the period of April 2007 –May 2009.

I also declare this bonafide work or a part of this work was not submitted by me or any other for any award, degree, diploma to any university, board either in India or abroad.

This is submitted to the TamilNadu Dr.M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulation for the DM Cardiology Degree examination.

Govt. Rajaji Hospital and
Madurai Medical College
Madurai.

Dr.V.Ravi

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INTRODUCTION

"When you solve one difficulty, other new difficulties arise. You then try to solve them. You can never solve all difficulties at once"

- P.A.M.CHIRAC

It is this spirit of learning more about how echocardiography can be used to evaluate Right ventricle function in pulmonary hypertension patients, which helps us. With multivarious etiologies causing pulmonary hypertension, making an accurate diagnosis, evaluating for the cause, monitoring the disease course and detecting complications of the disease has always been a challenge. Selecting the most appropriate for screening, diagnosing and monitoring the disease has been a subject of controversy.

Although there is no consistent and large data available in India revealing the exact incidence and prevalence of the disease, the increase in disease burden is certainly palpable and will continue to increase with time. With high mortality rates if left untreated and with very little treatment options in our hands, it definitely poses a challenge to the

medical fraternity for an early diagnosis and intervention before complications intervene. Most common cause of death in pulmonary hypertension is right ventricular failure. Unfortunately most patients present to us too late for any kind of meaningful intervention.

So as physicians, it is important for us to play a critical role in the evaluation of the use of appropriate diagnostic procedures and therapy modalities in the early detection and treatment of this disease. Rigorous and expert analogues of the available data that document the relative benefits and risks of the procedures can produce helpful guidelines that improve the effectiveness of care optimize patient outcomes and favourably affect the overall cost of care through a focus of resources on the most effective strategies.

REVIEW OF LITERATURE

BACKGROUND

Pulmonary Hypertension is a distinct clinical entity characterised by sustained elevation in Pulmonary artery pressure leading to right ventricular failure and death. Abnormalities in right ventricular function are known to occur in patients with pulmonary arterial hypertension and be detected at an early stage by Doppler echocardiography[1].

There is not much of data available from studies conducted in India regarding utility of Echocardiography in studying Right ventricle function in Pulmonary Hypertension patients. Right ventricle (RV) dysfunction is an important element in determining prognosis in Pulmonary Hypertension patients. Identification of early RV dysfunction is of utmost clinical importance because two-thirds of the deaths in Pulmonary Hypertension (PH) patients are attributable to RV failure[2,3]. The essential noninvasive test in the screening and evaluation of Pulmonary Hypertension (PH) is Doppler echocardiography. Echocardiography can

help not only to estimate right ventricular function, but also exclude the presence of left-heart disease. Doppler assessments can be used to estimate the right ventricular systolic pressure (RVSP) and to evaluate for the presence of intracardiac shunts and other forms of congenital heart disease [4,5]. Studies by Tei et al. have confirmed the close correlation of echocardiographically estimated pulmonary arterial pressure and Doppler derived right ventricle indices like Myocardial performance Index, with invasive measurements in patients with pulmonary hypertension [6,7,8.9].

A thorough understanding of the pertinent facts regarding pulmonary hypertension is absolutely necessary before treading into its complexities in treatment and management. The changing concepts about pulmonary hypertension mandate the review of the current literature of pulmonary hypertension.

Recently, parameters for normal pulmonary arterial systolic pressure derived by echo Doppler studies have been published which suggest that the upper limit of normal of pulmonary arterial systolic pressure in the general population may be higher than previously appreciated [10]. Importantly, however, the study characterized changes based on age and found a modest increase in pulmonary arterial pressure

with age similar to what exists in the systemic circulation.

DEMOGRAPHICS

Data regarding the prognostic implications of demographic variables such as age, gender, and time of onset of symptoms to diagnosis are inconsistent. The National Institute of health (NIH) Registry was the first large-scale evaluation of prognostic factors in Idiopathic pulmonary hypertension (IPAH). Age, time from onset of symptoms to diagnosis, and gender were not predictive of survival. In a retrospective, single center, uncontrolled case series of 61 patients with IPAH from India, younger age was associated with a worse prognosis. It should be noted that this population was younger than that included in the NIH Registry (mean age, 24.6 ± 11.8 years as compared to 36 ± 15 years [± SD]). In a study that included patients with many etiologies of PAH who were treated with epoprostenol, older age at diagnosis indicated a worse prognosis for those above the median. This, however, may be confounded by the inclusion of patients with the scleroderma spectrum of disease who tend to be older and also had a worse prognosis. A national survey of IPAH was conducted in Israel and identified 44 patients with a mean age of 43 ± 13 years (±

SD). Although they did not find age to be a prognostic variable, longer time of onset from symptoms to diagnosis was associated with a worse prognosis.

DEFINITION OF PULMONARY HYPERTENSION

Pulmonary arterial hypertension is defined as a sustained elevation of pulmonary arterial systolic pressure to more than 25 mm Hg at rest or to more than 30 mm Hg with exercise, with a mean pulmonary-capillary wedge pressure and left ventricular end-diastolic pressure of less than 15 mm Hg [11].

The pressure within the pulmonary arterial system may be increased for one of two reasons – increased flow or increased resistance within the pulmonary circulation, both of which lead to progressive and irreversible changes in the pulmonary vascular bed to result in chronic pulmonary hypertension.

PATHOLOGY OF PULMONARY HYPERTENSION [12,13]

Pulmonary endothelial cell and/or vascular smooth muscle dysfunction is the probable underlying basis for most forms of pulmonary hypertension. Morphological abnormalities in each cell line of the pulmonary vasculature have been described in cases of IPAH. The

endothelium in particular displays marked heterogeneity in the pulmonary vascular bed. Vascular alterations in pulmonary hypertension involve the entire arterial tree (Fig-1) and include:

1. **Main elastic arteries,** atheromas similar to those in systemic atherosclerosis;
2. **Medium-sized muscular arteries,** proliferation of myointimal cells and smooth muscle cells, causing thickening of the intima and media with narrowing of the lumina; and
3. **Smaller arteries and arterioles,** thickening, medial hypertrophy, and reduplication of the internal and external elastic membranes

Smooth muscle cell hypertrophy and increased connective tissue and extracellular matrix are found in the large muscular and elastic arteries. In the subendothelial layer, increased thickness may be the result of recruitment and/or proliferation of smooth muscle–like cells. Various growth factors are involved in the smooth muscle hypertrophy. (Fig -2) They are1.Prostaglandins 2.Nitric Oxide 3.Endothelin 4.Serotinin 5.Angiotensin II. These stimulatory signals by different pathways trigger the smooth muscle hypertrophy.

There are three significant pathways which are involved in the

pathogenesis of PAH[14] (Fig-3). They are

1. ENDOTHELIN Pathway
2. NITRIC OXIDE Pathway
3. PROSTACYCLIN Pathway.

ENDOTHELIN Pathway[15]

Endothelin (ET) is a potent mitogenic and vasoconstrictor peptide that also plays a role in the regulation of pulmonary vascular tone. ET-1 is the predominant isoform of endothelin in the cardiovascular system, generated through the cleavage of pre-pro ET-1 to big ET-1 and then to ET-1. ET-1 biosynthesis is regulated by physiochemical factors such as blood flow, pulsatile stretch, hypoxia, and thrombin. Endogenous inhibitors of ET-1 synthesis include nitric oxide and prostacyclin. ET-1 exerts its major vascular effects through activation of two distinct G protein–coupled ET_A and ET_B receptors. ET_A receptors induce vasoconstriction and cellular proliferation by increasing intracellular calcium. ET_B receptors are localized on endothelial cells and to some extent on smooth muscle cells and macrophages. The activation of ET_B receptors stimulates the release of nitric oxide and prostacyclin and prevents apoptosis.

NITRIC OXIDE Pathway[16]

Endothelial NO synthase is found in the vascular endothelium of the normal pulmonary vasculature. It generates nitric oxide from the vascular endothelium in response to shear stress, bradykinin and thrombin from L-arginine which is present in endothelium. No inhibits the growth of vascular smooth muscle cells by increasing the cGMP levels. Endothelial dysfunction causes reduced endothelial NO synthase which leads to smooth muscle hypertrophy.

PROSTACYCLIN Pathway[17]

Prostaglandins I_2 (PGI_2) and E_1 (PGE_1) are active pulmonary vasodilators, whereas PGF_{2a} and PGA_2 are pulmonary vasoconstrictors. Prostacyclin functions through cell-surface G protein–coupled receptors linked to different signaling pathways. Prostacyclin is a powerful vasodilator and inhibitor of platelet aggregation through activation of cyclic adenosine monophosphate (cAMP).Prostacyclin release prevents smooth muscle proliferation.Impaired prostacyclin release causes cellular proliferation and vasoconstriction.

An Apoptosis-Based Theory for the Development of PAH [18](Fig—4)

The central focus of this hypothesis is that apoptosis shows aspatio-temporal diversity within the vascular wall as PAH develops. An abnormality in the BMP[Bone Morphogenitic Protein] axis, inherited or acquired, will promote the apoptosis of Pulmonary Artery Endothelial Cells [PAEC], particularly in response to injury (viral infection, increased shear stress,etc). Initial PAEC death will cause loss of small capillaries (which are essentially PAEC tubes), increasing the flow and shear stress in the remaining vessels, amplifying the effect. The emergence of apoptosis-resistant PAECs expressing survivin will lead to the proliferation in the intima and in plexogenic lesions. At the same time loss of PAECs would allow for exposure of PASMCs [Pulmonary Smooth Muscle Cells] to circulating growth factors .Such factor, PDGF has been shown to induce the expression of survivin in the vascular smooth muscle cells. Survivin itself also induces the production of PDGF in human vascular smooth muscle cells. This positive feedback allows for amplification of the survivin pathway and thus the resistance to apoptosis. In summary, early PAH is characterized by increased apoptosis in the

endothelial layer. In contrast, late PAH is characterized by suppressed apoptosis and increased proliferation in both the intima and the media.

ROLE OF SEROTININ [19,20.]

Elevated plasma levels of serotonin and reduced platelet serotonin concentration have been described in IPAH patients. The abnormality in platelet serotonin handling is a primary process in the evolution of their pulmonary hypertension. Mutations in the serotonin transporter and 5-hydroxytryptamine 2B ($5\text{-}HT_{2B}$) receptor have now been reported in patients with IPAH.

GENETICS OF PAH [21] **(Fig—5)**

Bone Morphogenetic Protein Receptor Type 2 Gene is an important gene in the mediating the PAH.Mutations in BMPR-2 gene resulting in a predisposition to proliferation small pulmonary arteries. TGF-b pathway mediated through *BMPR-2* is critical for the maintenance and normal response to injury of the pulmonary vasculature.

5-HTT expression is elevated in cultured pulmonary artery smooth muscle cells from patients with PAH and that proliferation was also increased and related to 5-HTT expression and 5-HTT activity. 5-HTT is

encoded by a single gene on chromosome 17q11.2,

CLASSIFICATION AND STAGING OF PULMONARY HYPERTENSION

Pulmonary hypertension can occur from diverse etiologies and number of attempts has been made to classify the disease. The original classification, established at a World Health Organization (WHO) symposium in 1973, classified pulmonary hypertension into groups based on the known cause, i.e. secondary and defined primary pulmonary hypertension (PPH) as a separate entity of unknown cause. PPH was then classified into three histopathological patterns:

(a) Plexogenic arteriopathy (b) Recurrent thromboembolism and

(c) Venoocclusive disease.

In 1998, a new classification for pulmonary hypertension was developed that focused on the biologic expression of the disease and etiologic factors in an attempt to group these illnesses on the basis of clinical similarities. This classification serves as a useful guide to the clinician in organizing the evaluation of a patient with pulmonary hypertension and developing a treatment plan.

In 2003 the Third World Symposium updated the classification

system, notably dropping the term "primary" altogether. They also stressed that the staging of patients with PH should be based on the functional capacity of the patient rather than on hemodynamic parameters. The World Health Organization classification system, a modified form of the New York Heart Association functional classification system, was recommended by the Symposium as the preferred staging system. The NYHA functional classification (NYHA-FC) has been of prognostic importance to predict survival in PH.

Revised Clinical Classification of Pulmonary Hypertension[22] (Venice 2003)

Pulmonary arterial hypertension (PAH)

1.1. Idiopathic (IPAH)

1.2. Familial (FPAH)

1.3. Associated with (APAH):

1.3.1. Collagen vascular disease

1.3.2. Congenital systemic-to-pulmonary shunts

1.3.3. Portal hypertension

1.3.4. HIV infection

1.3.5. Drugs and toxins

1.3.6. Other (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy)

1.4 Associated with significant venous or capillary involvement

1.4.1 Pulmonary veno-occlusive disease (PVOD)

1.4.2 Pulmonary capillary hemangiomatosis (PCH)

2. Pulmonary hypertension with left heart disease

2.1. Left-sided atrial or ventricular heart disease

2.2. Left-sided valvular heart disease

3. Pulmonary hypertension associated with lung disease and/or hypoxemia

3.1. Chronic obstructive pulmonary disease

3.2. Interstitial lung disease

3.3. Sleep-disordered breathing

3.4. Alveolar hypoventilation disorders

3.5. Chronic exposure to high altitude

3.6. Developmental abnormalities

4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease

4.1. Thromboembolic obstruction of proximal pulmonary arteries

4.2. Thromboembolic obstruction of distal pulmonary arteries

4.3. Non-thrombotic pulmonary embolism (tumor, parasites, foreign material)

5. Miscellaneous:

Sarcoidosis, histiocytosis-X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

The functional classification patterned after the New York Heart Association Functional Classification for heart disease was developed to allow comparisons of patients with respect to the clinical severity of the disease process.

WHO Functional Classification of Pulmonary Hypertension

Class I – Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain

Class II – Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary

physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.

Class III – Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.

Class IV – Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may be present even at rest. Discomfort is increased by any physical activity.

NYHA-Functional classification (NYHA-FC) has been included in several studies of patients with PAH, and has been used in two ways in these reports: as a variable that might be predictive of survival in patients with PAH, and as an outcome to assess the impact of therapies for PAH. Because NYHA-FC relies on patient reporting of symptoms as an outcome, it may hold special importance for patients themselves, but it is also useful for clinicians trying to assess prognosis and response to therapy in patients with PAH.

NYHA-FC has been associated with improved survival in several

studies, but was found to be a significant predictor of mortality in only four studies. The NIH cohort study showed that among 194 patients who received a diagnosis showed that the risk of death was higher among patients in NYHA-FC III or IV than among those in NYHA-FC I or II[23]. The median survival time among NYHA-FC I or II patients was nearly 6 years, compared with 2.5 years for patients in NYHA-FC III and 6 months for patients in NYHA-FC IV. In a subsequent cohort study of 44 patients with IPAH, patients who were in NYHA-FC IV at the time of diagnosis had a significantly higher risk of death than patients in NYHA-FC I, II, or III. In another retrospective study of 51 patients with IPAH, patients in NYHA-FC III or IV had a shorter survival time than patients in NYHA-FC II. A third study of 91 patients with PAH, demonstrated that patients who were in NYHA-FC IV (compared with NYHA-FC I, II, and III patients combined) had a significantly decreased survival. In summary, higher NYHA-FC (III or IV) is associated with increased mortality both in treated and untreated patients with IPAH; in those receiving therapy, failure to improve NYHA-FC or deterioration in NYHA-FC, in and of itself, may be predictive of poor survival.

The initial evaluation of patients with PH should consist of testing

to confirm the diagnosis, a search for causative disorders and complications from the disease, and a determination of the severity of the disease.

EVALUATION OF A PATIENT WITH SUSPECTED PULMONARY HYPERTENSION

Essential Evaluation	**Contingent Evaluation**
History and physical examination	Transesophageal echo (TEE)
Chest x-ray (CXR)	Echo with bubble study
Electrocardiogram (ECG)	CT chest ± high resolution
Pulmonary function testing(PFT)	Pulmonary angiogram
Ventilation-perfusion scan (V/Q)	Arterial blood gas
Transthoracic echo (TTE)	Cardiac MRI
Blood tests: HIV, TFTs, LFTs, ANA	Blood tests: Uric acid, BNP
Six-minute walk test (6MWD)	Polysomnography
Overnight oximetry	Cardiopulmonary exercise
Right heart catheterization (RHC)	Open lung biopsy

Left-heart disease, valvular heart disease, and parenchymal lung disease deserve special attention during this initial period of evaluation as they are common causes of pulmonary arterial pressure elevation and right ventricular failure.

A detailed history should be taken from the patient in an attempt to define the severity, duration, and degree of acceleration in symptom severity. The patient should also be questioned about drugs of abuse,

herbal medicines and supplements, and prescription drugs including appetite suppressants and anorexigens.

CLINICAL FEATURES

Patients with PH usually present with nonspecific symptoms including dyspnea (60%), chest pain (40%), and fatigue. Symptoms are typically related to inability to increase cardiac output sufficiently in response to exertion and suboptimal oxygen transport[24]. The onset of right ventricular failure, manifest by a reduction in cardiac output and/or elevation in right atrial pressure, is usually associated with a marked clinical deterioration and poor prognosis. The rapidity in which this occurs in highly variable and is often related to the age of onset and associated conditions. Thus, patients with pulmonary arterial hypertension associated with congenital heart defects will more commonly have a slow, insidious onset of symptoms and develop right heart failure after decades, whereas patients with the CREST syndrome present later in life with a progressive downhill course.

Studies by **Harjai et al**. in 2002 indicate that right ventricle dysfunction in pulmonary hypertension occurs much before clinical examination can detect or ECG evidence of right heart abnormality

surfaces. Such class of patients are the ideal candidates for Doppler echocardiography screening for RV dssynchrony.

History and physical examination should focus on signs and symptoms compatible with an underlying disease including collagen vascular diseases, liver disease, sleep apnea, thromboembolic disease, and abnormalities in thyroid function.

The cardiac examination may reveal signs such as an increased pulmonic component of the second heart sound, an early systolic ejection click, a right ventricular fourth heart sound, a right ventricular heave, elevation of the jugular venous pulsations, or a murmur of either pulmonic or tricuspid insufficiency; however, none of these findings is specific to PH.

In addition to undergoing a careful cardiac examination, the patient should be questioned about congenital heart disease and previous catheter ablation therapy for atrial fibrillation, a procedure that has been associated with pulmonary vein stenosis and PH.

ELECTROCARDIOGRAM

The electrocardiogram (ECG) may be suggestive of right ventricular hypertrophy or right atrial enlargement and may demonstrate a

right axis deviation. The sensitivity and specificity of the ECG for detecting PH are sufficiently poor to preclude its use as a screening tool; however, patients with newly diagnosed PH should have at least 1 ECG to establish a baseline for future comparison.

In a study of 51 patients with untreated IPAH, several ECG variables, including increased P-wave amplitude in lead II, qR pattern in lead V_1, and World Health Organization criteria for RV hypertrophy were associated with an increased risk of death[25]. The prognostic value of these factors remained even after controlling for PVR.

Although all patients with pulmonary hypertension had echocardiographic evidence of right ventricle dyssynchrony, there was no change in the QRS complex duration.

CHEST X RAY

Right ventricular or pulmonary artery enlargement may be demonstrated on chest x-ray. Chest x-ray typically shows central enlargement of the pulmonary arteries with peripheral "pruning." **Lupi and colleagues** have described an index of PH based on the ratio of the summed horizontal measurements of the pulmonary arteries from midline

to their first divisions, divided by the transverse diameter. Chest radiography can be extremely helpful in identification of coexisting conditions such as COPD, kyphoscoliosis, and interstitial lung disease that may be responsible for the PH.

COMPUTERISED TOMOGRAPHY OF THE CHEST

In most cases, a CT scan of the chest with high-resolution cuts should be performed to evaluate for the presence of parenchymal lung disease and mediastinal disorders that could cause obstruction of the pulmonary vessels.

LUNG SCINTIGRAPHY

A ventilation-perfusion (V/Q) scan should be performed to evaluate for chronic thromboembolic disease. Prior studies have shown that V/Q scans have a high sensitivity and specificity for distinguishing between IPAH and chronic thromboembolic PH. Patients with a normal V/Q scan likely need no further evaluation for thromboembolic disease, but the poor correlation between the findings on V/Q scanning and the severity of vascular obstruction demands that those patients with a positive scan be sent for pulmonary angiography to accurately define the degree of

vascular obstruction and to identify patients who would benefit from surgical thromboendarterectomy.

In addition to basic testing such as a complete blood count (CBC), an arterial blood gas (ABG), and a complete metabolic panel, the initial laboratory evaluation for patients with PH should include thyroid function tests, liver function tests (LFT), testing for collagen vascular diseases, and testing to detect the human immunodeficiency virus.

PULMONARY FUNCTION TEST[26]

All patients with PH should undergo baseline pulmonary function testing including spirometry, determination of lung volumes, and evaluation of the diffusion limitation for carbon monoxide (DLCO). Pulmonary function testing may reveal evidence of significant obstructive or restrictive ventilatory defects that may be relevant to the etiology of PH.

SIX MINUTE WALK TEST[26]

Quantification of exercise tolerance is often performed by measuring the distance that a patient can walk in 6 minutes (6MWD). The 6MWD is a useful tool for following patients over time and, for this reason, serial determinations of the 6MWD distance should be made. The

6MWD has been used to evaluate patients and has been utilized as a primary end point in recent clinical trials since earlier trials showed that 6MWD was predictive of survival in patients with IPAH. Arterial oxygen desaturation > 10% during 6MWD has been shown to predict a 2.9 times increased risk of mortality over a median follow-up of 26 months.

PULSOXIMETRY

Screening for unsuspected nocturnal hypoxemia and sleep apnea should also be performed in those patients newly diagnosed with PH. No further testing is warranted if overnight oximetry on room air shows no desaturation. Abnormal oximetry necessitates a full polysomnogram to formally diagnose and determine the severity of sleep apnea, as nocturnal hypoxia may be an aggravating or even a causative factor for PH.

Mechanisms of exercise limitation in PH include arterial hypoxemia, poor cardiac output and stroke volume in response to increased demand, lactic acidosis at low work rates, and V/Q mismatching. Cardiopulmonary exercise testing provides more physiologic information than the standard 6MWD; however, because it is technically more difficult, is time-consuming, is not available at all centers, and may be less sensitive at detecting responses to treatment, it is

not routinely used. Patients with PAH typically show reduced peak VO_2, reduced peak work rate, reduced anaerobic threshold, reduced peak oxygen pulse, increased VE and VCO_2 slope indicating inefficient ventilation, and reduced ratio of VO_2 increase to work rate increase.

RIGHT HEART CATHETERISATION

Right heart Catheterisation (RHC) is initially performed for the purpose of diagnosing PH; other important information can also be obtained from this test. The right atrial pressure, the mixed venous oxygen saturation, the cardiac output and index, and the pulmonary vascular resistance all may be either measured or calculated during RHC[27]. If a congenital heart defect or a left-to-right shunt is suspected, one may measure the oxygen saturation at several points throughout the course of the systemic venous system, right heart, and pulmonary arterial system looking for a step-up in saturation that would suggest the presence of a left-to-right shunt. Pressure measurements obtained during RHC have been used to derive a prediction equation that has been used to assess "predicted survival" and long-term effects of new treatments on survival.

The equation to predict survival based on the National Institutes of Health (NIH) registry data is:

$$P(t) = [H(t)]^{A(x,y,z);}\ H(t) = [0.88 - 0.14t + 0.01t^2];\ A(x,y,z) = e^{(0.007325x + 0.0526y - .3275z)}$$

where P(t) = a patient's chances of survival at 't' years; t = 1, 2, or 3 years; x = mean pulmonary artery pressure; y = mean right atrial pressure; and z = cardiac index.

If RHC confirms the diagnosis of PH, a vasodilator should be given to determine the degree of pulmonary arterial vasoreactivity, a factor that carries therapeutic and prognostic significance, as will be discussed later. No consensus exists regarding which agent should be used to perform this test; however, intravenous epoprostenol, intravenous adenosine, or inhaled nitric oxide is often chosen because all of these are potent yet short-acting vasodilators. If the administration of a vasodilator causes the mean pulmonary arterial pressure to decrease ≥ 10 mmHg and reach ≤ 40 mmHg, with an unchanged or increased cardiac output, the patient is said to be vasoresponsive. The main reason for vasodilator testing is to identify patients who are likely to have a good long-term response to treatment with calcium channel blockers (CCBs) alone. Patients with

IPAH are more likely to have a positive vasodilator response than those with PAH associated with collagen vascular diseases. Overall, only a minority of patients (approximately 10% to 15%) are likely to have a positive vasodilator response.

MRI AND OPEN LUNG BIOPSY

The most recent recommendations from the ACCP did not advocate the routine use of magnetic resonance imaging (MRI) or open lung biopsy in the evaluation of patients with newly diagnosed PH. Cardiac MRI may provide additional pressure estimates and estimates of right ventricular mass and volume; however, at present the incremental value of this tool over standard testing measures is not sufficiently high to recommend its use in all patients.

Likewise, because of the risks associated with the procedure, The American College of Chest Physicians (ACCP) recommends lung biopsy "only if a specific question could be answered by tissue examination" in patients with PH and its "routine use to diagnose PH or determine its cause is discouraged." Such indications could include the detection of pulmonary veno-occlusive disease, bronchiolitis, active vasculitis, or pulmonary capillary hemangiomatosis.

BIOMARKERS

Candidate serum biomarkers that have been studied to evaluate and assess prognosis in IPAH include atrial naturetic peptide (ANP), brain naturetic peptide (BNP), catecholamines, and uric acid (UA). Nagaya and colleagues [28,29] studied 63 consecutive patients with Idiopathic Pulmonary Hypertension (IPAH) between 1994 and 1999. Patients with IPAH underwent blood sampling at the time of baseline catheterization and subsequently treated with vasodilators. Patients were followed up for a mean follow-up period of 24 months. Plasma ANP and BNP levels were low in control subjects, and both were increased and correlated with functional class in patients with IPAH. ANP and BNP levels were also correlated with mean right atrial pressure (mRAP), mean pulmonary artery pressure (mPAP), cardiac output (CO) and total pulmonary resistance (TPR). Among the noninvasive parameters studied (NYHA-FC, echocardiographic parameters, and plasma levels of ANP, BNP, and catecholamines), only BNP was found to be an independent predictor of survival. Additionally, follow-up measurements were performed at 3 months after receiving prostacyclin therapy in 53 patients. Changes in plasma BNP levels correlated closely with changes in right ventricle end

diastolic pressure (RVEDP) and TPR. BNP level at 3 months was found to be an independent predictor of mortality. Two studies assessed the relationship between plasma norepinephrine and mortality in patients with IPAH, and it was not found to be an independent predictor of mortality in either. Zaloga et al. showed that elevations in plasma NE are coincident with the presence of noncardiogenic pulmonary hypertension and that acute pharmacologic reduction of PVR does not normalize the loss of pulmonary NE metabolism.

Increased Uric Acid levels are believed to reflect impaired oxidative metabolism, since tissue hypoxia depletes adenosine triphosphate with degradation of adenosine nucleotides to compounds including UA. Since UA levels were shown to be associated with a poor prognosis in other disorders, investigators studied the association between serum UA levels and prognosis in patients with IPAH. Nagaya et al studied 102 consecutive patients over a long period of time. Follow-up was concluded in June 1998, for a mean duration of follow-up of 31 ± 37 months. Ninety-four percent of these patients were in NYHA-FC III or IV. Thirty age-matched, healthy volunteers served as control subjects. UA

levels were significantly elevated in patients with IPAH as compared to control subjects for each gender group and the group as a whole. Serum UA levels increased in proportion to the severity of the functional class and correlated with CO, TPR, and MVO_2. Among the noninvasive variables that were studied, serum UA levels were independently related to mortality.

Lopes and colleagues[30] reported that plasma von Willebrand factor antigen (vWF:Ag) is elevated in patients with IPAH, PAH associated with CHD, and other assorted disorders. von Willebrand factor is a large multimeric glycoprotein that is synthesized and stored in endothelial cells. Therefore, it was hypothesized that levels of von Willebrand factor could be elevated in patients with PAH due to the associated abnormalities in endothelial cell function. Lopes and colleagues studied 11 patients with IPAH and 24 patients with PAH associated with CHD over a 1-year period. Twenty healthy volunteers served as the control group. Treatment included anticoagulation, antiplatelet agents, and "anticongestive" measures. vWF:Ag was elevated in patients with PAH as compared to control subjects, and more so in patients with IPAH than with CHD.

Multivariate analysis showed that cause of PH and vWF:Ag levels were independently associated with survival.

ROLE OF ECHOCARDIOGRAPHY IN PULMONARY HYPERTENSION [31,32]

Pulmonary hypertension is easily recognized when the following M Mode and two dimensional echocardiographic features are present.

Diminished or absent ‘a’ (atrial) wave of the pulmonary wave.

Midsystolic closure or the notching of the pulmonary valve.

Enlarged chambers on the right side of the heart.

D-shaped left ventricular cavity caused by a flattened ventricular septum.

However, these features are not sensitive for pulmonary hypertension and are not predictive of right ventricle dysfunction. In a sense, these features are only qualitative and do not provide actual hemodynamic data.

Doppler echocardiography allows estimation of pulmonary artery pressures and PVR by measuring tricuspid regurgitation velocity, pulmonary regurgitation velocity and right ventricle outflow tract (RVOT)

flow velocity.

The American College of Chest Physicians (ACCP) Clinical Practice Guidelines emphasize the use of echocardiography in pulmonary arterial hypertension (PAH) with much of the discussion involving the estimate of right ventricular systolic pressure (RVSP). As indicated in the The American College of Chest Physicians (ACCP) consensus guidelines, Doppler echocardiography is the "test of choice" for noninvasive measurement of pulmonary arterial pressure in patients in whom PAH is clinically suspected.

Less widely recognized—and probably underemphasized in the clinical practice guidelines—is the value of echocardiography in assessing end-organ manifestations of severe PAH. Right ventricular failure is the most common cause of death in patients with PAH, and the results of several observational studies suggest that echocardiographic evaluation of right ventricular structure and function can provide important prognostic information[33]. A Doppler-derived index of right ventricular myocardial performance (MPI) that represents the sum of isovolumetric contraction and relaxation times divided by the ejection time. This index of global right ventricular function was a potent and independent predictor of

cardiac death and lung transplantation.

Abnormalities in the Doppler flow velocity patterns of right ventricular ejection (due to increased right ventricular impedance) and left ventricular filling (due to abnormal ventricular interaction) are common findings in patients with severe PAH. In patients with PH, a short right ventricular acceleration time (<62 ms) and a ratio of early to late transmitral flow velocities (E/A) <1 were associated with reduced survival.

Structural manifestations of right ventricular decompensation- right atrial enlargement (RAE) and paradoxical displacement of the interventricular septum (IVS) were indicative of a poor prognosis in patients with PAH and WHO Class III or Class IV symptoms. A planimetered right atrial area in the apical four-chamber view exceeding 20 cm^2/m and a value >2 for the end-diastolic eccentricity index—a simple measure of septal displacement measured from the parasternal short axis view—were also associated with a poor prognosis. The presence of a pericardial effusion, a common finding in patients with severe PAH that reflects an elevated right atrial pressure, was a powerful and independent predictor of mortality in PAH. In a series of 26 patients with Idiopathic PAH receiving conventional therapy, Eysmann and

colleagues studied 41 echocardiographic variables and 9 cardiac catheterization variables. Although several factors were prognostic on univariate analysis, multivariate life-table analysis of noninvasive variables revealed the severity of pericardial effusion to be independently significant ($p = 0.006$). In an analysis of 79 of 81 Idiopathic PAH patients who participated in the randomized trial of IV epoprostenol, pericardial effusion was noted in 43 patients (54%). Patients with larger effusions generally had more severely impaired exercise performance. Larger effusion size was also correlated with more RA dilatation, greater displacement of the intraventricular septum during diastole, and more TR than patients with no or trace effusion. Although there was not an association between pericardial effusion and mortality at the end of the 12-week study, effusion size was correlated with death ($p = 0.02$).

Therefore, there is ample evidence to support a comprehensive echocardiographic examination to assess the extent of target organ disease as an important component of the routine evaluation. The assessment by an experienced echocardiographer of the degree of right ventricular enlargement and dysfunction, utilizing simple measures—the presence of a pericardial effusion, an E/A ratio <1, a right ventricular acceleration

time <62 ms, a planimetered right atrial size >20 cm2/m, and a diastolic eccentricity index >2—or more complex parameters, such as the Doppler right ventricular index or the Tei Index, can complement the clinical evaluation in assessing prognosis and guiding therapy.

PROGNOSIS IN PULMONARY HYPERTENSION AS RECOMMENDED BY ACCP[34]

In patients with Pulmonary hypertension, the following parameters, as assessed at baseline, may be used to predict a worse prognosis, as suggested by The American College of Chest Physicians.

Advanced NYHA-FC. Quality of evidence: good; net benefit: substantial; strength of recommendation: A.

Low 6MWT distance. Quality of evidence: good; net benefit: substantial; strength of recommendation: A.

Presence of a pericardial effusion. Quality of evidence: good; net benefit: substantial; strength of recommendation: A.

Elevated mRAP. Quality of evidence: fair; net benefit: substantial; strength of recommendation: A.

Reduced CI. Quality of evidence: fair; net benefit: substantial; strength of recommendation: A.

Elevated mPAP. Quality of evidence: fair; net benefit: intermediate; strength of recommendation: B.

Elevated Doppler Echocardiography RV (Tei) index. Quality of evidence: low; net benefit: intermediate; strength of recommendation: C.

ECG findings of increased P-wave amplitude in lead II, qR pattern in lead V_1, and World Health Organization criteria for RV hypertrophy. Quality of evidence: low; net benefit: intermediate; strength of recommendation: C.

Elevated BNP (> 180 pg/mL). Quality of evidence: low; net benefit: intermediate; strength of recommendation: C.

Patients with IPAH treated with epoprostenol, persistence of NYHA-FC III or IV status after at least 3 months of therapy may be used to predict a worse prognosis. Quality of evidence: fair; net benefit: substantial; strength of recommendation: A.

Patients with scleroderma-associated PAH, reduced DLCO (< 45% of predicted) may be used to predict a worse prognosis. Quality of evidence: low; net benefit: small/weak; strength of recommendation: C.

In pediatric patients with IPAH, younger age at diagnosis may be used to predict a worse prognosis. Quality of evidence: low; net benefit: small/weak; strength of recommendation: C.

ECHOCARDIOGRAPHIC VIEWS OF THE RIGHT HEART[35]

Owing to the complexities in the geometry of the right heart, no single view is sufficient to visualize the right heart. The RV inflow is best seen with anterior and medial angulation of the transducer in the standard parasternal long axis view. The parasternal short axis view is useful for visualizing the base of the right heart, RA and IAS, RV outflow tract, pulmonary valve and MPA and its branches. Forward and regurgitant flow in pulmonary valve is seen in this view. Geometry and motion of the right ventricle is seen from the apical four chamber view. Doppler interrogation of tricuspid regurgitation is optimal in this view.

ECHOCARDIOGRAPHIC INDICES FOR RIGHT VENTRICLE DYSFUNCTION – A PERSPECTIVE MYOCARDIAL PERFORMANCE INDEX – TEI INDEX [36,37].

Studies have found several novel echocardiographic and Doppler measurements of RV function to be risk factors for heart failure, independently of traditional risk factors. For example, Myocardial Performance Index (MPI) provided prognostic information beyond that of other measurements of cardiac function and traditional risk factors.

MPI has previously been shown to have prognostic value in patients with dilated cardiomyopathy, amyloidosis, coronary heart disease and symptomatic heart failure as well as in the general population. MPI provides prognostic information independently of other measurements of cardiac function and of traditional risk factors for heart failure. Therefore, MPI seem to be a clinically relevant measurement of global ventricular function and may prove to be a valuable tool in assessing the risk of developing right heart failure.

Our knowledge of the natural history of heart failure indicates that both asymptomatic systolic and diastolic dysfunction can precede the onset of overt heart failure. The utility of Myocardial Performance Index (MPI) is comparable to simultaneous cardiac catheterization measurements of right ventricular function as the MPI was found to reflect both systolic and diastolic function.

MPI mirrors both the depolarization and repolarization process. It seems like changes in cellular Ca^{2+} handling in the myocardium underlie much of the abnormal contractility and relaxation. In the failing heart, the

contraction and relaxation becomes slower explaining why MPI increases with deterioration of cardiac function. There is evidence that sub-clinical depolarization (and repolarization) defects to be early phenomena in the natural history of heart failure as noted above.

Myocardial performance Index is a unitless number reflecting the global performance of the ventricle. It was devised in the mid 1990's (Tei et al). It is a simple index which incorporates both systolic and diastolic parameters and can be applied to either left or right ventricle. Several studies have used this index as a prognostic indicator of left ventricular performance. The utility of MPI as an indicator of global RV performance is an area of interest in the recent past.

The ratio of isovolumic contraction time(IVCT) and ejection time (ET) was closely correlated to $+dP/dt$ (reflecting systolic function) and the ratio of isovolumic relaxation time(IVRT) and ejection time was closely correlated to $-dP/dt$ (reflecting diastolic function). Therefore, MPI may be considered the sum of an index reflecting systolic function and an index reflecting diastolic function. Thus, the superior predictive capacity of MPI could be explained by the fact that MPI reflects global function, while other measurements are limited to reflect mainly either LV systolic

or diastolic function.

$$MPI = \frac{IVCT + IVRT}{ET}$$

According to the above equation, systolic dysfunction is characterized by the prolongation of IVCT and decrease in ET. Whereas the diastolic dysfunction is characterized by the lengthening of IVRT. Presence of both is indicated by an increase in MPI. The normal value of MPI of Left ventricle is 0.39 +/- 0.08.

MPI is helpful in risk stratification of patients with pulmonary hypertension. For the right heart, the normal values are 0.28 +/- 0.04. An increase in the right ventricle MPI is a very sensitive and specific marker of pulmonary hypertension. Thus MPI is of value in patients in whom tricuspid regurgitation is either not present or cannot be quantified to assess the severity of pulmonary hypertension.

Thus, MPI is a reliable and easily assessable measurement of global ventricular function, and as such, suitable for large-scale examinations. Nevertheless, further studies are needed in order to define the role of MPI in clinical practice. Clinically significant age- and gender-specific cut-off

points need to be defined; furthermore it has to be determined if pharmacological and/or non-pharmacological interventions lower MPI and whether lowering MPI modifies the risk associated with a high MPI.

ISOVOLUMETRIC CONTRACTION TIME (IVCT) & ISOVOLUMETRIC RELAXATION TIME (IVRT)

Isovolumetric phase is the earliest phase of ventricular systole in which the ventricle contracts as a closed chamber without any change in the volume of the chamber. The isovolumic contraction time corresponds to when calcium enters the myoplasm from the sarcolemma.

Traditionally IVRT is recorded as the aortic valve closure and mitral valve opening time in the Left ventricle. M Mode echocardiography and pulsed wave Doppler were used for this purpose. Normal values approximates 65 +/- 20 msec. Isovolumic relaxation time reflects the removal of Ca^{2+} from the myoplasm by Ca^{2+}-ATPases.

Recently continuous wave Doppler echocardiography has been used to measure IVRT. The Apical 5 chamber view is used for this

purpose. Measurements made by this method is comparable to that made by invasive methods. IVRT represents the earliest phase of ventricular diastole. Abnormalities of this index has been described as a non invasive predictor of diastolic dysfunction. However, measurement of IVRT as the sole indicator of diastolic dysfunction is limited, since no information on ventricle filling is provided.

RIGHT VENTRICLE SYSTOLIC FUNCTION

Right ventricle systolic function can be evaluated in several ways. It is affected in several situations like Inferior myocardial infarction, pulmonary hypertension and arrhythmogenic right ventricular dysplasia. As with left ventricle, wall motion abnormality can be assessed in RV. Both right ventricle free wall and IVS should be evaluated. It provides a qualitative assessment of RV systolic function. A more quantitative approach involves the measurement of right ventricle volume and area at end diastole and end systole. RV area fractional shortening and Ejection fraction can be calculated. This can be measured using the M mode echocardiography from the apical 4 chamber view.

RIGHT ATRIAL AND RIGHT VENTRICLE DIMENSIONS IN ECHOCARDIOGRAPHY

For several reasons, the right heart anatomy and function is a complex one and has not been well studied. The right atrium is abnormal in both right ventricle volume and pressure overload states and RV failure. It is best visualised in echocardiography by the apical 4 chamber view or the sub costal view. RA dimensions can be measured in 2 ways. The Linear dimensions in 2 different axes and planimetry method are currently used. Another qualitative method of assessing RA size is to compare it with the Left atrium size. If the RA size is greater than the LA size, then RA enlargement is inferred.

Right ventricle dimension assessment is very difficult for the following reasons. Firstly, the complex anatomical shape – cresentic shape of the cavity. Secondly, the presence of irregular endocardial surface. Thirdly, the complexity in its contraction mechanics, comparable to that of bellows. Lastly its location immediately behind the sternum also poses a problem in the evaluation of RV anatomy and function.

RV is cresentic in its minor axis, but along its long axis it is complex. There is no simple geometric three dimensional figure accurately represents this chamber. Contraction is also complex as mentioned above. Relatively small movements produce large ejection volumes. Normally the RV is two thirds of the size of Left ventricle.

To measure the RV dimensions and volumes, both the area – length and Simpson's rule has been employed. The area – length method measures: the estimate of short axis and a linear measure of length from the apical 4 chamber view. Recently three dimensional echocardiography has resolved the problem in the techniques that assumptions about the shape to be made and also there was a lack of gold standard for comparison.

RIGHT VENTRICULAR ABNORMALITES IN PULMONARY HYPERTENSION[38]

The role of RV is to deliver oxygen deficient blood to the gas exchange membranes of the pulmonary circulation. Under normal circumstances, there is little impedance with the resistance only about $1/10^{th}$ of that in the systemic circulation. Consequently a very low

pressure gradient of only 5mmHg is required to pump blood into the pulmonary circulation. In addition the pressure overload on the right ventricle is prevented by the recruitment of newer vessels and distension of the compliant vessels in the pulmonary circulation.

Right ventricular performance is influenced by contractile state of the myocardium and extrinsic factors, including loading conditions, LV performance, pericardial constraint, coronary perfusion, function of the IVS and intrapericardial pressure. In the setting of pulmonary diseases, it is the alteration of loading conditions that is the greatest influence on the heart

Pathophysiologic response of the right ventricle or dysfunction of the right heart can be due to pressure overload, volume overload and ischemia. Distinguishing between them is a key factor in ascertaining the etiology of the RV failure[39]. The hemodynamic response to pulmonary vascular diseases causing pulmonary hypertension is a pressure overload state.

Pressure overload of RV results in hypertrophy of both the RV free wall and the IVS. This is often associated with increase in the trabeculations of the right ventricle. The parasternal long axis view is used for the measurement of RV free wall thickness. RV pressure overload also results in the flattening of the interventricular septum. It is the result of abnormal pressure gradient between the left and right ventricle. A characteristic feature of the RV pressure overload is the presence of the flattening of IVS through out the cardiac cycle in contrast from the RV volume overload where the flattening is a feature only in diastole[40].

Weimann et al demonstrated the mechanism of paradoxical septal motion in patients with right ventricular volume overload (RVVO) [41]. Short axis cross-sectional, echocardiographic studies of the left ventricle (LV) and interventricular septum (IVS) were performed in patients with paradoxical septal motion due to RVVO and in normal subjects. Short axis study in normal subjects revealed the left ventricle to be a relatively circular structure during both diastole and systole. In patients with RVVO a change in LC diastolic shape was observed. This change in shape varied

from a slight flattening of the LV and IVS during diastole to total reversal of the normal direction of septal curvature such that the IVS became concave toward the RV and convex toward the LV. During systole the LV and IVS returned to their normal relatively circular configuration. This change in LV shape from diastole to systole resulted in net motion of the IVS toward the right ventricle (paradoxically). This study therefore suggests that paradoxical septal motion in patients with right ventricular volume overload is a result of a change in the diastolic shape of the left ventricle. In patients with RV pressure overload, the IVS paradoxical motion persisted through out the cardiac cycle.

Doppler imaging is also very useful in RV pressure overload. Pulmonary valve flow and tricuspid regurgitation velocity can be measured[42]. The acceleration time is the time from onset to peak velocity which provides a rough estimate of increase in pulmonary artery pressure. The shorter the acceleration time, greater is the pulmonary artery pressure. Tricuspid regurgitation develops early in RV dysfunction, although severe regurgitation develops only in severe RV failure.

In patients with severe pulmonary hypertension, RV is dilated when viewed from the apical 4 chamber view. A subjective criterion for RV dilatation is a right ventricular diastolic area equal to or greater than that of the left ventricle. RV dilatation is also observed in conditions producing right ventricle volume overload conditions. Such conditions can be differentiated from those produced by RV pressure overload by a high eccentricity index that persists only in diastole and normalizes in systole. Eccentricity index is derived from the ratio of two orthogonal minor axis measured from the short axis view. The normal value is 1.0. In conditions producing septal flattening, index is greater than 1.0.

PULMONARY ARTERY SYSTOLIC AND DIASTOLIC PRESSURES[42]

A more direct measure of the RVSP is done by measuring the tricuspid regurgitation jet velocity. Bernoulli s equation is used to calculate the pressure gradient between RV and RA.

Then RVSP is calculated by

$$\mathbf{RVSP = 4\ (TR_{velocity})^{2} + P_{RA}}$$

Where $TR_{velocity}$ is the maximum velocity of the TR jet in m/sec and P_{RA} is the pressure in RA.

With pulmonary hypertension, pulmonary artery diastolic pressure increases disproportionately creating a high pressure gradient and hence an increased end-diastolic regurgitant velocity. Thus in pulmonary hypertension, pulmonary regurgitant velocity at end diastole is >2 m/sec.

LIMITATIONS OF DOPPLER ECHOCARDIOGRAPHY

Studies have demonstrated that the concordance between Doppler echocardiography and direct measurement via RHC worsens as the pressure rises, with poorest correlation when the systolic pulmonary pressure is over 100 mmHg. Doppler echo may also overestimate systolic PAP in a population comprising people with normal pressure.

AIMS AND OBJECTIVES

To study the clinical profile of Idiopathic Pulmonary Hypertension patients.

To study the utility of echocardiography in assessing the right ventricular function in patients with idiopathic pulmonary hypertension.

To measure the Pulmonary artery systolic pressure in Idiopathic Pulmonary hypertension using Doppler Echocardiography.

To assess the structural abnormalities of the heart in patients with idiopathic pulmonary hypertension.

To study the correlation between the clinical grading of severity and echocardiographic grading of pulmonary hypertension.

MATERIALS AND METHODS

About 50 patients who got admitted to the Department of Cardiology and Medicine in Govt Rajaji Hospital, Madurai between April 2007 and May 2009 were chosen and studied.

The type of study : **analytical study**

Selection criteria and study population :

Inclusion criteria

Fifty patients (mean age 27.64±8.18 years, 44 females) who were admitted to our hospital and found to have Pulmonary Hypertension of obscure/unknown etiology underwent a complete clinical and echocardiographic examination. In the population studied, pulmonary hypertension of varying severities was detected, as determined by Doppler echocardiography.

Exclusion criteria

Pediatric age group patients were not included in the study. Patients with Chronic Obstructive pulmonary Disease, cardiomyopathy, abnormal

left ventricular systolic function, valvular heart disease or congenital heart disease with Left to right shunt lesions were all excluded.

The Institutional ethical committee approved the study and all patients gave informed consent to undergo evaluation.

Methods :

All the patients included in the study were subjected to detailed history taking and complete physical examination. They were also evaluated for the etiology for pulmonary hypertension with complete blood count (CBC), Renal function testing (RFT), Liver function testing (LFT), Thyroid function testing (TFT), HIV ELISA, Anti nuclear antibodies (ANA), Chest X Ray, USG abdomen, High resolution Computed Tomography of the Chest (HRCT) ,Pulmonary function testing (PFT).

Clinical grading of pulmonary hypertension severity was done according to the WHO functional classification.

All patients underwent a complete transthoracic echocardiographic study including two-dimensional, M Mode, color flow and spectral

Doppler using ALOKA SSD 4000 and PHILIPS IE-33 echocardiography machine. Continuous ECG monitoring of the patients was done during the procedure with the patient lying in standard left lateral decubitus procedure.

Standard two-dimensional echocardiographic evaluation of right atrium (RA) and right ventricle (RV) size and function was performed. The right atrium and right ventricle were visualized by the apical four chamber view (fig 6). RA size was evaluated using linear dimensions in the minor axis. Modified Simpson's rule was employed for estimating RV area (fig 7). In addition, right ventricular end-diastolic (RV EDA) and end-systolic areas (RV ESA) were measured from the apical 4-chamber view to calculate right ventricular fractional area change (RV FAC). The main pulmonary artery (MPA) was optimally visualized using the parasternal short axis views. The pulmonary artery size was measures below the pulmonic valve (fig 8). M mode and two Dimensional echocardiography were used to document presence or absence of pericardial effusion (fig 9). The free fluid in the pericardial cavity was visualized as an echo-free space using the parasternal long axis and short

axis views. Isovolumetric contraction time (IVCT) (fig-10), isovolumetric relaxation time (IVRT) (fig-11) and ejection time (ET) (fig-12) were measured across the tricuspid valve using the pulsed wave Doppler echocardiography during the tricuspid valve flow and subsequently right ventricular Myocardial Performance Index (MPI) or the Tei index was calculated using the standard formula MPI = IVCT+IVRT / ET.

Paradoxical septal motion was visualized in the parasternal long axis view (fig-13) and the 'D' sign was visualized by the parasternal short axis view as a flattening of the septum (fig 14). Pulmonary artery systolic pressures (PASP) were estimated using the approach of calculating the systolic pressure gradient between right ventricle and right atrium by the maximum velocity of the tricuspid regurgitant jet in continuous wave (Fig 15&16). Doppler study using the modified Bernoulli equation and then adding to this value an estimated right atrial pressures based on both the size of the inferior vena cava and the change in caliber of this vessel with respiration. M mode echocardiography was used to study the 'a' wave of the pulmonary valve and midsystolic notching or closure of the valve (fig 17). Contrast study with agitated normal saline was done to rule out

congenital or acquired shunt lesions (Fig 18&19). All the patients in our study had normal left ventricular systolic function and normal valves.

The reference limits for various echocardiographic indices and parameters used in this study were adopted from the standard echocardiographic manuals. The diagnosis of pulmonary hypertension and severity grading was done as follows:

Pulmonary Artery Systolic Pressure (PASP) measured > 25 mmHg at rest was considered to be pulmonary hypertension.

Variable	MILD	MODERATE	SEVERE
PASP mmHg	25-50	51-75	>75

The reference limits for the main pulmonary artery (MPA) diameter measured below the pulmonary valve:

Variable	Reference range	Mildly Dilated	Moderately dilated	Severely dilated
Pulmonary artery size, cm	1.5 – 2.1	2.2- 2.5	2.6-2.9	≥ 3.0

The reference limits for Right atrial (RA) minor axis dimension measured in apical four chamber view are:

variable	Reference range	Mildly enlarged	Moderately enlarged	Severely enlarged
RA minor axis dimension, cm	2.9 – 4.5	4.6 – 4.9	5.0 – 5.4	≥ 5.5

The reference limits used for the myocardial performance index for the right ventricle is **0.28 ± 0.04.**

The reference limits used for right ventricle end systolic area (RV ESA), right ventricle end diastolic area (RV EDA) and right ventricle fractional area change (RV FAC) are as follows:

Variable	Reference range	Mildly abnormal	Moderately abnormal	Severely abnormal
RV diastolic area, cm^2	11 – 28	29 – 32	33 – 37	≥38
RV systolic area, cm^2	7.5 – 16	17 – 19	20 – 22	≥23
RV fractional area change %	32 – 60	25 – 31	18 – 24	≥17

M mode and 2 D echocardiography measurements of the echo-free space were used to grade the severity of pericardial effusion.

variable	Mild	Moderate	large
Echo free space, cm	<1	1 – 2	>2

Statistical Tools

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer using Epidemiological Information Package (EPI 2002).Using this software, frequencies, percentage; mean, standard deviation, $\mathbf{x^2}$ and **'p'** values were calculated. A **'p'** value less than 0.05 is taken to denote significant relationship.

RESULTS

The results of clinical evaluation of the 50 patients are shown below. The table 1 and Fig 20 show the age wise distribution of IPAH in our study. The mean of age of patients in our study is 27.64 ± 8.18 years.

Table 1

Age wise distribution of the disease

Age (In Years)	Cases	
	No.	%
Less than 20	6	12
20-24	18	36
25-29	6	12
30-34	8	16
35-39	6	12
40 & above	6	12
Total	50	100
Mean S.D.	27.64 yrs 8.18 yrs	

The number of patients belonging to each WHO functional class is shown in Table 2 and Fig 21.

Table 2

WHO Functional Classification

WHO Class	**Cases**	
	No.	**%**

I	-	-
II	12	24
III	22	44
IV	16	32
Total	50	100

The table 3 below shows there is no statistical correlation between WHO functional class severity and age of the patients.

Table 3

Relationship between WHO functional classification and Age

WHO Classification	Age in years	
	Mean	**S.D.**
II	24.5	7.12
III	30	9.27
IV	26.75	7.23
'P'	0.4748 (Not significant)	

The table 4 and Fig 22 show the sex wise distribution of the disease. Of the 50 patients, 44 (88%) were females and 6 (12%) were males.

Table 4
Sex Distribution

Sex	Cases	
	No.	**%**
Male	6	12
Female	44	88
Total	25	100

All the patients in WHO functional class II (n=12) were females.

About 91% of the patients in class III (n=22) were females and 9% were males. Class IV (n=16) had 75% females and 25% males. The table 5 shown below illustrates the findings.

Table 5

WHO Classification and Sex

WHO Classification	Males		Females	
	No.	%	No.	%
II (6)	-	-	12	100
III(22)	2	9.1	20	90.9
IV (16)	4	25	12	75

The table 6 shows the common symptoms in our study population. Dyspnea on exertion is the most common symptom and was found in all our patients (100%). Fatigue is the second most common symptom in our patients (68%).

Table 6

Symptoms

Symptoms	No.	%
Dyspnea on exertion	50	100
Chest Pain	20	40
Giddiness	22	44
Syncope	4	8
Cough / Sputum	30	60
Palpitations	26	52

Pedal edema	26	52
Hemoptysis	10	20
Fatigue	34	68

The correlation between the number of symptoms at the time of presentation and WHO functional class severity was statistically significant (p = 0.0228).

Table 7

WHO Classification and number of symptoms present

WHO Classification	Number of symptoms present	
	Mean	S.D.
II	5.0	1.41
III	3.82	1.25
IV	5.63	1.06
'p'	0.0228 (Significant)	

Among the 50 patients, 46 patients (92%) showed some abnormality in the complete blood count (CBC) and anemia was the most common abnormality and CBC was normal in the rest. 48 patients (96%) showed ECG abnormalities in the form of sinus tachycardia, right atrial enlargement and right ventricular hypertrophy and right axis deviation

(fig- 23). 46 patients (92%) showed chest X ray evidence of pulmonary artery dilatation (fig- 24). 2 patients (4%) showed evidence of apical fibrosis of right lung and 2 patients (4%) had a normal CXR.

The renal function testing, liver function testing and thyroid function testing revealed no abnormalities in the study population. HIV ELISA and anti nuclear antibodies were negative in all the patients included in our study. High resolution computed tomography of the chest showed no abnormalities of the pulmonary parenchyma and ruled out the possibility of pulmonary thromboembolic disease in our patients (fig -25).

The table 8 shows the echocardiograpic parameters measured to assess right heart structural changes and functional abnormalities. The mean size of the right atrium was 4.69 ± 1.22 cm. The right ventricle dimension as determined using Simpson's rule rule had a mean value of 28.93 ± 8.45 cm^2 . The mean PASP in our patients was 92.52 ± 35.29 mm Hg. 10 patients (25%) had mild pulmonary hypertension, 4 patients (10%) had moderate pulmonary hypertension and 36 patients (65%) had severe pulmonary hypertension. The mean fractional area change in right ventricle is 18.48 ± 5.71 %. The mean value of MPI was 0.821 ± 0.205.

Table 8

Echocardiographic measurements in our patients

Parameter	Mean	S.D.
RA cm	4.69	1.22
RV cm^2	28.93	8.45
MPA cm	2.64	0.67
TRPG	82.52	35.29
PASP	92.52	35.29
RVESA	22.36	3.35
RVEDA	35.84	3.59
RVFAC	18.48	5.71
IVCT	82.08	14.14
IVRT	123.04	27.53
ET	256.7	41.2
MPI	0.821	0.205

Echocardiography showed all the patients included in the study showed features of absent ‘a’ wave and presence of mid systolic notch in the pulmonary valve. And 28 patients (56%) had pericardial effusion, 40 patients (80%) had paradoxical motion or flattening of the interventricular septum. Bubble study was negative in all the patients ruling out the possibility of abnormal left to right shunts.

The table 9 showed that the relationship between the RA size, RV size, Pulmonary artery size and the WHO functional class. Likewise the Table 10 shows statistically significant relationship between WHO

functional class and echocardiographic indices for RV dysfunction like RV FAC and MPI.

Table 9

Relationship between WHO Functional Classification and structural abnormalities

Parameter	WHO Classification						'p'
	II		III		IV		
	Mean	S.D.	Mean	S.D.	Mean	S.D.	
RA cm	2.98	0.48	5.03	0.86	5.5	0.69	0.0008 (Significant)
RV cm^2	15.05	2.79	32.34	3.29	34.67	1.54	0.0006 (Significant)
MPA cm	1.9	0.32	2.96	0.62	2.74	0.52	0.0041(Significant)

Table 10

Relationship between WHO Classification and Echocardiographic Indices

Parameter	WHO Classification						'p'
	II		III		IV		
	Mean	S.D.	Mean	S.D.	Mean	S.D.	
TRPG	39.17	7.52	81.72	21.8	116.13	25.46	0.0002(Significant)
PASP	49.17	7.52	91.73	21.8	126.13	25.46	0.0002(Significant)
RVESA	17.5	1.52	23.45	2.38	24.5	1.2	0.0012(Significant)
RVEDA	31.67	2.07	37.09	3.45	37.25	2.12	0.0059(Significant)
RVFAC	26.67	2.34	16.18	2.6	15.5	4.72	0.0016(Significant)
MPI	0.641	0.084	0.783	0.160	1.049	0.085	0.0001(Significant)

DISCUSSION

Demographic studies with respect to IPAH are very limited in India. According to one report, there are 2 cases per million population in the west. Exact incidence and prevalence rates could not be calculated from our study. There is a strong female preponderance in patients with IPAH. The male: female ratio in our study is approximately 1:7. The most common age group affected in our study population is in the 3rd and 4th decade in contrast to the reports from the west which have reported higher incidence of IPAH in 4th or the 5th decade. The reason for the early presentation in our study population is not known. The role of genes in determining the onset of disease and disease severity is still unsettled.

Most patients in our study shared the clinical presentation. Exercise intolerance in the exertional dyspnea and fatigability are the most common clinical manifestations in our study populations. 100 % of our patients has dyspnea as opposed to 60 % reported in another study. Other common symptoms include chest pain (40%), cough (60%) giddiness

(44%) and pedal edema (52%). The number of symptoms at the time of presentation has an effect on the severity of the disease. Patients with more clinical symptoms belong to higher WHO functional class and has higher values of PASP.

Echocardiography developed over the last three decades has become an extension of the physical examination in the modern evaluation of a patient with heart disease. The review of the various studies shows this unique non invasive technique is useful in knowing the anatomical and pathophysiological alterations and in the hemodynamic evaluation of any case of disease leading to heart failure.

The results of this study suggest that right ventricular dysfunction, represented by both structural and pathophysiological abnormalities occur in patients with pulmonary hypertension. Right ventricular abnormalities occurred even with mild elevations of pulmonary artery pressure. In addition, they correlate well with markers of disease severity including pulmonary hypertension severity index, World Health Organization functional class. ($p < 0.05$)

Among the structural abnormalities, the right ventricle dimension had a higher statistically significant correlation of WHO functional class severity ($p = 0.0006$) when compared to RA size ($p = 0.0008$) and MPA size ($p = 0.0041$).

The results of this study can be quite useful in the evaluation of chronic pulmonary hypertension patients given the well-known limitations of standard echocardiography in the assessment of right ventricular size and function due to the complex structure and asymmetrical shape of this cardiac chamber. The changes in right ventricular area obtained from the apical 4-chamber views were taken as indices of right ventricular size and global systolic function rather than ventricular volumes and ejection fraction, which appeared to be influenced by many factors. In addition RV Myocardial Performance Index, a well-recognized measure of global ventricular systolic and diastolic function that is independent on any geometric assumptions and heart rate was calculated from IVCT, IVRT and ET.

In our study, Myocardial Performance Index is found to have the highest correlation to WHO functional class severity ($p = 0.0001$). RV FAC ($p = 0.0016$) and PASP ($p = 0.0002$) also show statistically significant correlation to WHO class. Thus MPI is the most sensitive and specific marker of RV dysfunction in patients with pulmonary hypertension.

The value of MPI has been widely applied in previous studies to quantify regional left ventricular myocardial function under different clinical scenarios and all the available evidence suggests that it is quite useful to assess left ventricular performance. However, despite all this knowledge on left ventricular mechanical activation, a few attempts have been made to quantify right ventricular dyssynchrony using these indices. In our study, we evaluated this index to assess RV function and use them as a marker of severity of pulmonary hypertension.

Presence of paradoxical septal motion is also a well-recognized marker of right ventricular deformation by either pressure or volume loads. The variability in our measurements of RV size, morphology, and

functional performance in patients with variable degree of chronic pulmonary hypertension is probably due to the right ventricular geometric remodeling that occurs in these patients with pulmonary hypertension as described by Sukmawan et al.

Areas of further work are required in tissue Doppler imaging (TDI) which might be useful in the early identification of patients with sub clinical evidence of right ventricular dysfunction but further studies are required. In addition, the long-term effects of right ventricular dysfunction on morbidity and mortality as well as whether right ventricular resynchronization therapy that might correct right ventricular dysfunction and restore right ventricular function with resultant improvement of markers of disease severity and functional capacity also require investigation.

There are patients whose resting hemodynamics are normal, but in whom marked elevations in pulmonary pressure occur with exercise. It has been presumed that this represents an early stage of pulmonary vascular disease. However, as patients may have a hypertensive response to exercise with respect to the systemic vasculature, a similar type of response can occur in the pulmonary vasculature. Thus, whether exercise

induced pulmonary hypertension represents true pulmonary vascular disease or reduced compliance of an otherwise normal pulmonary circulation can be difficult to ascertain and this is one area where further research is yet to take off.

LIMITATIONS OF THE STUDY

Several important limitations of these studies should be acknowledged. The number of patients are relatively small in our study; However, even with this small number of patients we are able to reach our primary goal of identifying the presence of a statistically significant right ventricular mechanical dysfunction in patients with pulmonary hypertension.

We have evaluated patients with the available investigations for PAH and they are incomplete. An invasive pressure measurement is not used in this study; therefore, assessments of right ventricular time-pressure plots, dp/dt, and pulmonary vascular resistance are not available to compare with our echo data.

Similarly, peak systolic pulmonary arterial pressures are estimated simply based on tricuspid regurgitation measurements. However, this widely used Doppler-derived pressure estimation is well recognized and has been documented to have a good correlation with simultaneously obtained catheter-derived measurements; particularly in patients with

elevated systolic pulmonary artery pressures.

The use of fractional area change as an index of global right ventricular systolic function has a limitation of being highly afterload dependent particularly in patients with pulmonary hypertension. This effect might be compounded by tricuspid regurgitation that by reducing systolic afterload augments right ventricular systolic function.

Nonetheless, the very consistent theme that has emerged is that echocardiographic evidence of right ventricular failure is an ominous finding. Additional research to further define the role of echocardiography in assessing prognosis and guiding therapy in patients with PAH would be of value.

CONCLUSIONS

We conclude that our study population also has a strong female preponderance and has a relatively earlier onset of the disease in the 3rd or the 4th decade.

The study also indicates that right ventricular abnormalities occurs in patients with chronic idiopathic pulmonary hypertension and is strongly correlated with right atrial dimensions, right ventricular size and main pulmonary artery size, which are all increased with increasing severity in pulmonary hypertension.

Other structural abnormalities in pulmonary hypertension include presence of pericardial effusion, paradoxical septal motion of IVS and pulmonary valve abnormalities (absent 'a' wave and presence of mid systolic notch or closure).

In addition, right ventricular functional abnormalities including RV FAC and RV MPI are associated with disease severity and it correlates well with pulmonary hypertension severity index, World Health Organization class. RV FAC decreases with increase in severity of

pulmonary hypertension and MPI increases with increases with increase in PASP.

Right ventricular dysfunction is clearly evident even with mild elevations in the pulmonary artery systolic pressure and Doppler echocardiography is the test of choice in patients suspected to have Idiopathic Pulmonary artery hypertension.

BIBLIOGRAPHY

1. Meluzin J, Spinarova L, Dusek L, Toman J, Hude P, Krejci J: Prognostic importance of the right ventricular function assessed by Doppler tissue imaging. Eur J Echocardiogr 2003;4:262-271.
2. Barnard D, Alpert JS: Right ventricular function in health and disease, Curr Probl Cardiol 1987, 12:417-449.
3. Angel López-Candales , Kaoru Dohi , Navin Rajagopalan , Matthew Suffoletto , Srinivas Murali , John Gorcsan and Kathy Edelman. Right ventricular dyssynchrony in patients with pulmonary hypertension is associated with disease severity and functional class. Cardiovascular Ultrasound 2005, 3:23: 1186 – 1196.
4. M.A. Higham, D. Dawson, J. Joshi, P. Nihoyannopoulos and N.W. Morrell. Utility of echocardiography in assessment of pulmonary hypertension secondary to COPD. Eur Respir J 2001; 17:350-355.
5. Schiller NB: Pulmonary artery pressure estimation by Doppler and two-dimensional echocardiography. Cardiol Clin 1990, 8:277-28.
6. Tei C. New noninvasive index for combined systolic and diastolic ventricular function. J Cardiol 1995; 26: 135-136.

7. Tei C, Ling LH, Hodge DO, et al. New index of combined systolic and diastolic myocardial performance: a simple and reproducible measure of cardiac function-a study in normals and dilated cardiomyopathy. J Cardiol 1995; 26: 357-366.
8. Tei C, Nishimura RA, Seward JB, Tajik AJ. Noninvasive Doppler derived myocardial performance index: correlation with simultaneous measurements of cardiac catheterization measurements. J Am Soc Echocardiogr 1997; 10: 169-178.
9. Bruch C, Schmermund A, Marin D, et al. Tei-index in patients with mild-to-moderate. Congestive heart failure , Eur Heart J 2000;21:1888-1895.
10. Marc Humbert Pulmonary and Critical Care Updates Update in Pulmonary Arterial Hypertension 2007 Am J Respir Crit Care Med Vol 177. pp 574–579, 2008.
11. Gaine SP, Rubin LJ. Primary pulmonary hypertension. Lancet 1998;352:719-725.
12. Rubin M. Tuder, MD, John C. Marecki, PhD, Amy Richtera, Iwona Fijalkowska PhD Pathology of Pulmonary Hypertension, Clin Chest Med 28 (2007) 23–42.

13. Giuseppe G. Pietra, Frederique Capron, Susan Stewar, Marc Humbert, Ivan M. Pathologic assessment of vasculopathies in pulmonary hypertension J. Am. Coll. Cardiol. 2004;43;25S-32S.
14. Humbert M,Sitbom O,Simonneau G;Treatment of pulmonary arterial hypertension, N engl J Med 351;1425.2004.
15. Giaid A, Yanagisawa M, Langleben D, et al. Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. N Engl J Med 1993;328:1732-173.
16. Mason NA, Springall DR, Burke M, et al. High expression of endothelial nitric oxide synthase in plexiform lesions of pulmonary hypertension. J Pathol 1998;185:313-318.
17. Tuder RM, Cool CD, Geraci MW, et al. Prostacyclin synthase expression is decreased in lungs from patients with severe pulmonary hypertension. Am J Respir Crit Care Med 1999;159:1925-1932.
18. Evangelos D. Michelakis Spatio-Temporal Diversity of Apoptosis Within the Vascular Wall in Pulmonary Arterial Hypertension: Heterogeneous BMP Signaling May Have Therapeutic Implications, Circ. Res. 2006;98;172-175.

19. Lee SL, Wang WW, Lanzillo JJ, Fanburg BL. Serotonin produces both hyperplasia and hypertrophy of bovine pulmonary artery smooth muscle cells in culture. Am J Physiol 1994;266:L46-L52.
20. Eddahibi S, Humbert M, Fadel E, et al. Serotonin transporter overexpression is responsible for pulmonary artery smooth muscle hyperplasia in primary pulmonary hypertension. J Clin Invest 2001;108:1141-1150.
21. John H. Newman, Richard C. Trembath, Jane A. Morse, Ekkehard Grunig, James E. Loyd, Serge Adnot, Fabio Coccolo, Carlo Ventura, John A. Phillips, III, Genetic basis of pulmonary arterial hypertension: Current understanding and future directions, Am. Coll. Cardiol. 2004;43;33S-
22. Simonneau G, Galie N, Rubin LJ, et al. Clinical classification of pulmonary hypertension. J Am Coll Cardiol 2004;43:Suppl S:5S.
23. Pulmonary Arterial Hypertension in France Results from a National Registry Am J Respir Crit Care Med Vol 177. pp 574–579, 2008.
24. Libby et al, Braunwalds Heart Disease; A Textbook of Cardiovascular Medicine,8/ed.
25. Bossone, E, Paciocco, G, Iarussi, D, et al The prognostic role of the

ECG in primary pulmonary hypertension. Chest 2002;121,513-518

26. Oudiz RJ,Barst RJ et al ;Cardiopulmonary exercise testing and six minute walk correlations in pulmonary arterial hypertension;Am J Cardiol97;123,2006.
27. Donald S Baim.Grossmans Cardiac atheterization, Angiography and Intervention 7th ed.
28. Nagaya, N, Nishikimi, T, Uematsu, M, et al Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. Circulation 2000;102,865-870.
29. Nagaya, N, Uematsu, M, Satoh, T, et al Serum uric acid levels correlate with the severity and the mortality of primary pulmonary hypertension. Am J Respir Crit Care Med 1999;160,487-492.
30. Lopes, AA, Maeda, NY, Goncalves, RC, et al Endothelial cell dysfunction correlates differentially with survival in primary and secondary pulmonary hypertension. Am Heart J 2000;139,618-623
31. Feigenbaum H. Echocardiography. Sixth edition. 2005.
32. Jae k Oh . The Echo Manual. Third edition. 2006.
33. S.Z. Turkistani, J. Rhodes, A. Banerjee, N.G. Pandian.

Echocardiographic Assessment of the Right Ventricular Response to Exercise. Pediatric Cardiology 2001;22: 107-109.

34. McLaughlin VV, Presberg KW, Doyle RL, Abman SH, McCrory DC, Fortin T, Ahearn G, American College of Chest Physicians: Prognosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 2004, 126(Suppl):78-92.

35. Catherine M Otto. The practice of clinical echocardiography. Second edition. 2002.

36. Thomas Menzel, MD, Thorsten Kramm, MD, Susanne Mohr-Kahaly, MD, Eckhard Mayer, MD, Hellmut Oelert, MD, Juergen Meyer, MD. Assessment of cardiac performance using Tei indices in patients undergoing pulmonary thromboendarterectomy. Ann Thorac Surg 2002;73:762-766.

37. Yeo TC, Dujardin KS, Tei C, Mahoney DW, McGoon MD, Seward JB. Value of a Doppler-derived index combining systolic and diastolic time intervals in predicting outcome in primary pulmonary hypertension. Am J Cardiol 1998; 81: 1157-1161.

38. Chin KM, Kim NH, Rubin LJ: The right ventricle in pulmonary hypertension. Coron Artery Dis 2005, 16:13-18.

39. Robert Naeije and Sandrine Huez Right ventricular function in pulmonary hypertension: physiological concepts European Heart Journal Supplements (2007) 9 (Supplement H), H5–H9.

40. J.G. Coghlan and J. Davar How should we assess right ventricular function in 2008?European Heart Journal Supplements (2007) 9 (Supplement H), H22–H28.

41. Weyman AE, Wann S, Feigenbaum H, Dillon JC: Mechanism of abnormal septal motion in patients with right ventricular volume overload: a cross-sectional echocardiographic study. Circulation 1976, 54:179-186.

42. Mizushige K, Morita H, Senda S, Matsuo H: Influence of right ventricular pressure overload on left and right ventricular filling in cor pulmonale assessed with Doppler echocardiography. Japan Circ J 1989, 53:1287-1296.

APPENDIX I – PRO FORMA

EVALUATION OF PATIENTS WITH PULMONARY HYPERTENSION

NAME: AGE: SEX: OCCUPATION:

ADDRESS: IP/OP NO: CD NO:

COMPLAINTS: WHO FUNCTIONAL CLASS -

1. DYSPNEA 2. CHESTPAIN 3. GIDDINESS

4. SYNCOPE 5. COUGH/SPUTUM 6. PALPITATIONS

7. PEDAL EDEMA 8. HEMOPTYSIS 9. FATIGUE

OTHERS:

PAST HISTORY:

SYSTEMIC HTN DM PUL TB BR ASTHMA

RHD IHD DRUG INTAKE

PERSONAL HISTORY: SMOKING ALCOHOL EXPOSURE TO STD

MENSTRUAL / OBSTETRIC HISTORY:

FAMILY HISTORY:

EXAMINATION:

GENERAL EXAMINATION:

VITALS : PULSE BP RR TEMP

CVS: JVP

RS:

INVESTIGATIONS

Hb % TC DC P L E M ESR HCt

BLOOD SUGAR UREA SERUM CREATININE

LIVER FUNCTION: THYROID FUNCTION:

HIV ELISA ANA USG ABDOMEN

CXR : HRCT:

PULMONARY FUNCTION TESTING: PULSEOXIMETRY

ECG IN ALL LEADS:

ECHOCARDIOGRAM:

TTE:

VALVES RA RV MPA AORTA
PERICARDIAL EFFUSION IVS PARADOXICAL MOVEMENT

TR PG PASP

LVEF

RV END SYST AREA RV END DIAS AREA

RV FRACTIONAL AREA SHORTENING

RVIDd RVIDs ED PRPG

IVCT ICRT ET MPI = IVCT+IVRT/ET

PULMONARY VALVE M – MODE

BUBBLE CONTRAST STUDY

TEE: